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Appendix 1

I hereby certify that the following is a true, correct and saccurate translation of the Russian text of RU 2 179 452 C1:

(PAGE 1)

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RUSSIAN AGENCY
FOR PATENTS AND TRADEMARKS

(12) The specification to the patent of the Russian Federation

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- (24) Date of the beginning of validity of the patent: 22.06.2000
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- (56) References: RU 2065307 C1,20.08.1996. RU 2105567 C1,
 20 27.02.1998. RU 2058153 C1, 20.04 1996. RU 2134589 C1,
 20.08.1999. RU 2097060 C1,27.11.1997.
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 Pak Vladimir Nikolaevich

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- (54) METHOD OF TREATMENT OF MALIGNANT NEOPLASMS AND COMPLEX PREPARATION HAVING ANTINEOPLASTIC ACTIVITY FOR USE IN SUCH TREATMENT
- 35 (57) Abstract

The invention relates to medicine, oncology in particular. It

has been proposed, depending on the character and seriousness of the disease, to inject parenterally to a patient, together with the basic infusion-detoxication therapy, the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a 5 polyene antibiotic, mainly amphotericin B or nystatin, in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler once within twenty-four hours at an interval of three days in course of 10 infusions. The complex preparation having antineoplastic activity comprises the following components, in 10 mg:AFP 0.07 - 0.15, a polyene antibiotic 4.2 - 7.0 and a filler 3.5 - 5.0. As a filler mainly polysaccharide selected from the group of rheopolyglukin*, polyglukin* or sugar, for example glucose, is used. The method enables to lower the doses of injectable medicines and to reduce the costs of treatment. The 15 complex preparation distinguishes by high efficiency a small number of antineoplastic activity, components, simplicity of preparation and a long term of storage. 2 independent and 2 dependent claims.

20 (PAGES 3 to 6)

The invention relates to the field of medicine, oncology in particular and can be used for chemotherapeutical treatment of oncological patients, suffering from different kinds of malignant neoplasms.

Methods of treatment of cancer by means of chemical preparations to mechanism of action chemical known. According preparations are subdivided into alkylating agents, 30 antimetabolites, alkaloids, antibiotics, hormones, immunomodulators and some others. In the course of treatment by different chemical preparations, the advantages and disadvantages thereof have been revealed.

Owing to comparatively small working concentrations, the 35 chemical preparations affecting DNA are widely used. Alkylation of the vital DNA molecule leads to incapability of normal

fission of cells and to their subsequent elimination. However, at the same time, DNA of normal non-cancerous cells is also subjected to alkylation. In order to reduce toxicity in relation to normal cells, when such preparations are applied, the 5 methods for targeted delivery of preparations to cancerous cells by means of specific ligands, for example alphafetoprotein (AFP), are used. AFP is a transport protein, capable of delivering the substance bounded thereto to the cells having corresponding receptors. Such receptors abound on actively 10 proliferating cancerous cells.

The method of treatment of primary liver cancer by means of intra-arterial injection of AFP in an amount of 2-20 mg, mainly 15 mg, five times at an interval of 7-12 days is known (Patent RU 2,058,153, cl. A 61 K 38/00, published April 20, 1996, Bull. 11).

The known method foresees the use of large amounts of AFP and distinguishes by long duration and limited extent of use, since the conditions for selecting patients for treatment by such a method are absence of jaundice and ascites, unoperability, absence of serious concurrent diseases.

The method of treatment of malignant neoplasms by means of intravenous injection of a complex preparation, comprising AFP and estrone-doxorubicin conjugate (Patent RU 2,026,688, cl. A 61 K 38/00, published January 20, 1995, Bull. 2), is known. For preparation of the complex preparation impure AFP, an abortive material is used which is concentrated after rough purification to the content of AFP of 100 µg/ml and is then sterilized. Thereafter an antineoplastic antibiotic - doxorubicin is subjected to conjugation with a ligand - estrone in an equimolar ratio. Immediately 1-2 hours before intravenous injection the concentrate of AFP in an amount of 100 ml is mixed with 20 ml of the conjugate and thus one dose of the complex preparation for one injection (a single dose of AFP comprises 10 mg) is

obtained. The overall course of treatment comprises 6 injections (three times every other day at an interval of a week).

The disadvantage of the known method is the use of high doses of AFP, the disadvantage of the known complex preparation is a labour-intensive procedure of obtaining the three-component complex AFP-estrone-doxorubicin and impossibility of storage of the preparation for more than 2 hours.

10 The closest method to the present method (the prototype) is a method of treatment of primary liver cancer, comprising injection of the preparation doxorubicin dissolved in Lipiodol ultrafluid into the liver artery, while as the preparation doxorubicin doxorubicin-estrone dissolved in 96% ethyl alcohol 15 at 70-76°C in a dose of 20-60 mg in 10-15 ml of Lipiodol ultrafluid is used. 20 minutes prior to that a dose of 2-10 mg of AFP in 12-15 ml of physiological salt is injected into the liver artery; the repeated treatment is carried out after 3-4 weeks (Patent RU 2,065,307, cl. A 61 K 38/17, published 20 August 20, 1996, Bull. 23).

The disadvantages of the known method are:

- labour-intensity of the method, connected with separated 25 injection of AFP and of doxorubicin-estrone complex;
 - the use of high concentrations of the chemical preparations (AFP-2-10~mg,~doxorubicin-estrone~complex-20-60~mg), which can lead to toxic side reactions;
 - high cost of treatment.

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The closest complex preparation to the present complex preparation (the prototype) is a kit used for treatment of primary liver cancer and comprising doxorubicin-estrone in an amount of 20-60 mg in 15 ml vials, Lipiodol ultrafluid in two ampules by 10 ml, AFP in an amount of 2-10 mg in 10 ml vials, physiological salt in volume of 15 ml in an ampule and 96% ethyl

alcohol in volume of 5 ml in an ampule (Patent RU 2,065,307, cl. A 61 K 38/17, published August 20, 1996, Bull. 23).

The disadvantages of the known kit are:

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labour-intensity and duration of obtaining the sterile doxorubicin-estrone complex as well as labour-intensity of preparation of the working solution of the given preparation: the preparation is dissolved in 0.5-1.5 ml of 96% ethyl alcohol, 100 heating to 70-76°C, the resultant solution is transferred into 10-15 ml of previously upwarmed Lipiodol ultrafluid, the suspension thus obtained is cooled to 32-37°C and is then injected into the liver artery under X-ray television control; high concentrations of the preparations used in the kit;
 polycomponent nature of the kit.

The technical object of the group of the inventions is to simplify the known method, to lower the doses of the preparations to be injected and to reduce the costs of treatment.

The established object has been achieved by means of hereby proposed method of treatment of malignant neoplasms and a complex preparation having antineoplastic activity for use in such treatment.

The realization of the method of treatment.

Depending on the character and seriousness of the disease, to a patient, together with the basic infusion-detoxication therapy, the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a polyene antibiotic in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler, is parenterally injected once within twenty-four hours at an interval of three days in a course of 10 infusions.

The complex preparation having antineoplastic activity comprises the following components, in mg:

AFP 0.07 - 0.15

a polyene antibiotic 4.2 - 7.0

5 a filler 3.5 - 5.0

As a polyene antibiotic amphotericin B or nystatin is mainly used.

10 As a filler sugars are mainly used, for example glucose or synthetic polymers, selected from the group of polysaccharides, for example polyglukin, rheopolyglukin and dextran.

The complex preparation is obtained as follows: AFP with purity not less than 98% is dissolved in distilled water or physiological salt in an amount of 0.07-0.15 mg/ml, whereto a polyene antibiotic in an amount of 4.2-7.0 mg/ml and then a filler in an amount of 3.5-5.0 mg/ml are added, after that the components are carefully mixed and the resultant mixture is then left to stand at 18-25°C for 10-12 hours. Thereafter the solution is sterilized by filtration, pre-packed in ampules or vials having a capacity of 1.2 or 3 ml and freeze-dried. The mass ratio of AFP, a polyene antibiotic and a filler is 1:(60-100):(50-70).

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The complex preparation (conventional designation Reducin) is a powder of yellow colour, soluble in water, in physiological salt, in glucose solution and in other diluents (carriers), suitable for intravenous injection. One ampule of the complex preparation comprises: 0.07-0.15 mg of AFP, 4.2-7.0 mg of polyene antibiotic and 3.5-5.0 mg of corresponding filler. For preparation of the working solution the content of the ampule is dissolved in 2-3 ml of sterile water and is then transferred into 200 ml vial together with a carrier, suitable for intravenous injection.

The present method comprises injection to a patient of a new complex chemical preparation having antineoplastic activity and consisting of a vector part (AFP), specific to cancerous nonspecific part, comprising a cytotoxic and a 5 substance. As the latter an essentially new channel-forming and surface-active agent (SAA), namely a polyene antibiotic, for example amphotericin B or nystatin, which have not been previously used as antineoplastic remedies, is used. The targets for the new complex preparation are membranes of substructures 10 intracellular substructures. Such mitochondria, lysosomes, endoplasmatic reticula (EPR), nuclei, etc. In case of disorders in the function of membranes of substructures, a normal cell function, ensurable by the compartmentalization of different functions, is impossible. As autodigestion of cancerous cells takes place 15 a result according to the mechanism of induced apoptosis.

The use of AFP as a vector for targeted delivery of cytotoxic preparations to cancerous cells is known (see for instance 20 patent RU 2,071,351, cl. A61 K 38/17, published January 10, 1997). In all known cases AFP is bounded with a cytotoxic part of the preparation by a chemical covalent bond, whereas in the present complex preparation AFP and SAA form a noncovalent stability of ensuring simultaneously the complex, 25 macromolecule during transportation and its functional independence in the process of cytotoxic action of the polyene antibiotic. The activity of the present complex preparation is based on the initiation of physiological reduction of cancerous cells according to the mechanism similar to that of apoptosis. 30 As a rule, the natural autodestruction of the cells of tumor under the influence of the present complex preparation does not lead to intoxication of the organism and the effect of the treatment appears quickly.

35 The essential distinctive features of the present method, as compared with those of the prototype, are:

- to a patient the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a polyene antibiotic in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler, is injected parenterally and simultaneously in a course of 10 injections (infusions) once in three days, which enables to simplify the known method, to lower the doses of the preparations to be injected and to reduce the costs of treatment.

The essential distinctive features of the present complex 10 preparation, as compared with those of the known preparation, are:

- the complex preparation comprises additionally a surfaceactive agent, namely a polyene antibiotic, mainly amphotericin

 15 B or nystatin, in an amount of 4.2-7.0 mg, which provides the
 complex with a new type of bond with a vector part with a
 noncovalent bond, and a new mechanism of interaction with
 cancerous cells with the membranes of the substructures of
 cancerous cells (membranes of lysosomes, EPR, mitochondria,
 20 nuclei), which, in its turn, improves the efficiency of the
 treatment and reduces side complications;
- the complex preparation comprises the components in optimal, experimentally selected amounts and ratios, namely: AFP 0.07-0.15 mg, a polyene antibiotic 4.2-7.0 mg, a filler 3.5-5.0 mg, which enables to improve the efficiency of the treatment and substantially lower the doses of the active components used.

Being supported by the fact that no analogous method of treatment of malignant neoplasms and no analogous complex preparation having antineoplastic activity have been revealed, it may be concluded that the present group of inventions meet the requirements for patentability in respect of "novelty" and "inventive step".

35 The present method has been tested on 8 patients having IV clinical stage of oncological diseases, progressing after

traditional ways of treatment. A full or a partial clinical effect has been achieved on 6 patients out of 8 (75%). The terms of remission were from 6 months to 1.5 years. In majority cases, for achieving a well-defined clinical effect it was sufficient to conduct one course of treatment.

The inventions are characterized by the following Examples.

Example 1

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For preparation of the complex preparation Reducin 700 mg of AFP, 42 g of amphotericin B and 50 g of rheopolyglukin are dissolved in 1 litre of distilled water by mixing, subsequently the volume is increased up to 10 litres. The resultant mixture is incubated at room temperature for 10-12 hours and is then subjected to sterilization by filtration through a membrane filter, pre-packed in 10,000 ampules or vials by 1 ml (a single dose) and thereafter freeze-dried in aseptic conditions. One ampule (vial) comprises 0.07 mg of AFP, 4.2 mg of amphotericin 20 B and 5.0 mg of rheopolyglukin.

Example 2

The complex preparation Reducin is obtained analogously to 25 Example 1, with the exception that to water solution 1 g of AFP, 50 g of amphotericin B and 40 g of polyglukin are added. As a result the preparation, comprising 0.1 mg of AFP, 5.0 mg of amphotericin B and 4.0 mg of polyglukin in a single dose, is obtained.

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Example 3

The complex preparation is obtained analogously to Example 1, with the exception that to water solution 1.5 g of AFP, 70 g of 35 amphotericin B and 30 g of dextran (molecular mass 100 kDa, Serva) are added. As a result the preparation, comprising 0.15

mg of AFP, 7.0 mg of amphotericin B and 3.0 mg of dextran in a single dose, is obtained.

Example 4

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The complex preparation is obtained analogously to Example 1, with the exception that to water solution 750 mg of AFP, 60 g of nystatin and 50 g of glucose are added. As a result the preparation, comprising 0.075 mg of AFP, 6.0 mg of nystatin and 10 5.0 mg of glucose in a single dose, is obtained.

Example 5

Patient L., 54 years old, the patient record 587, was 15 hospitalized on April 02, 1999 with the diagnosis: central cancer of the right lung IV stage (recidivation, progressive course), cancer of the left mammary gland II stage (remission). The patient was complaining weakness, dyspnea, exhausting cough.

The data of the inspection. X-ray photograph of the organs of thorax: on both sides in the lungs there are numerous polymorphous shadows of metastases in sizes from 0.5 to 2.5 cm and of medium intensity and uneven outlines. The shadow of mediastinum has shifted rightwards and expanded. The right lung field has diminished in volume; below the fourth rib there is an intensive overshadowing because of the liquid in the pleural cavity.

A course of polychemotherapy was conducted according to the scheme CAF: On the 1st and 8th days intravenously 1 g of cyclophosphane, on the 1st and 8th days intravenously 500 mg of 5-fluorouracil, on the 2nd and 9th days of the treatment intravenously 40 mg of adriablastin. The treatment was accompanied by high toxicity without an expressed clinical seffect.

Thereafter the patient was treated according to the present method. The complex preparation Reducin, comprising 0.07 mg of AFP, 4.5 mg of amphotericin B and 5.0 mg of glucose, was injected by infusion in a course of 10 injections once in three 5 days. The condition of the patient has improved and became satisfactory a week after the course of treatment had been finished. On the basis of the data of the radiology inspection of the organs of thorax favourable changes were registered, characterized by the decreased number of metastases in the lungs and the weakening of intensity of the shadows of dissemination. The liquid in the pleural cavity was not inspected. Dyspnea on ascent has diminished and cough disappeared completely. During the treatment with Reducin a rise in temperature and a shiver were observed, which were treated with standard preparations.

Example 6

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Patient M., 62 years old, the patient record 800, was hospitalized with the diagnosis: central cancer of the right 20 lung IV stage (adenocarcinoma); spread metastases in head, in the right hemisphere of brain, in neck, in thorax; right-sided carcinomatous pleurisy; chronic deforming bronchitis; pulmonary emphysema; diabetes of the 2nd type; IBO; angina of efford; secondary immunodeficiency, undernourishment, condition after 25 the courses of polychemotherapy.

The treatment program included a course of polychemotherapy according to the scheme CAMF. To the patient were injected 1 g of cyclophosphane on the 1st and 8th days, adriamicin on the 30 1st and 8th days, 50 mg of methotrexate on the 1st and 8th days, 5-fluorouracil on the 2nd and 9th days. The treatment was accompanied by endotoxicosis and an abrupt worsening of the condition of the patient. No positive effects were detected.

35 Because of complicated condition of the patient, to him intravenous infusions of the complex preparation Reducin,

comprising 0.075 mg of AFP, 5.0 mg of nystatin and 5.0 mg of rheopolyglukin in a single dose, in a course of 10 infusions once in three days were prescribed.

56 days after the beginning of the treatment according to the the diminishing of the sizes of subcutaneous present method metastases were noted. By the end of the treatment rapid improvement of the main disease was noted, which became apparent from the twofold reduction of the size of all surface metastatic 10 nodes, the disappearing of pains in the lower jaw, the decreasing of the rate of exudation in the right pleural cavity. Thrice conducted right-sided pleural punction proved the decreasing of volume of exudate: before the treatment the volume of exudate was 600 ml, a week after the treatment - 350 ml, three weeks after 15 the treatment - 20 ml. The improvement of function of central nervous system became apparent from restoration of normal swallowing function, restoration of gripping function of the left hand, clinically corresponding to the reduction of metastasis in the right hemisphere of brain.

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The use of the present method of treatmet of malignant neoplasms and the complex preparation having antineoplastic activity, as compared with the known method of treatment and the kit for use in such treatment, enables:

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- to simplify the method of treatment by means of simultaneous parenteral injection of the complex preparation, comprising AFP and cytotoxic SAA in optimal ratios;
- to lower the doses of the used components: AFP 13-140 times, 30 the cytotoxic component 3-14 times;
 - to improve the efficiency of treatment by means of using the complex preparation having high specifity to growing cancerous cells and optimal composition of the complex preparation having a long term of storage (two years);
- 35 to reduce the costs of treatment by means of using a small number of components in the complex preparation and low doses

of the chemical preparations to be used.

Thus, while using the present method of treatment of malignant neoplasms two biological mechanisms are realized. The first of 5them comprises the targeted delivery of the cytotoxic agent by means of AFP to tumorous cells. The second one comprises the directed destruction of the tumorous cells because of destruction of the intracellular structures, in particular EPR and lysosomes. This may be accompanied by autodigestion of tumorous cells, according to the mechanism of targetably induced apoptosis. The directed reduction affects much less the cells of blood-forming, immune and other constantly growing systems, being often damaged when standard antineoplastic chemotherapy is applied. The present scomplex preparation Reducin distinguishes by high efficiency of antineoplastic activity, a small number of components, simplicity of preparation and a long term of storage.

Claims:

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- 1. A method of treatment of malignant neoplasms, comprising injection of alpha-fetoprotein, characterised in that alpha-fetoprotein is injected as a component of the complex preparation comprising additionally a polyene antibiotic and a filler in 25 ratio of 1: (60-100): (50-70), and the preparation is injected parenterally in a course of 10 injections once in three days.
- 2. A complex preparation having antineoplastic activity, comprising alpha-fetoprotein , a cytotoxic substance and a sofiller, characterized in that the preparation comprises a polyene antibiotic as a cytotoxic substance and polysaccharide or sugar as a filler in the following quantitative ratio of the components, in mg:

AFP 0.07 - 0.15

35 a polyene antibiotic 4.2 - 7.0

a filler 3.5 - 5.0

- 3. A complex preparation of claim 2, characterized in that the preparation comprises amphotericin B or nystatin as a polyene antibiotic.
- 54. A complex preparation of claim 2, characterized in that the preparation comprises polysaccharide, selected from the group consisting of polyglukin, rheopolyglukin and dextran or sugar, mainly glucose as a filler.
- 10 * Note: In the present translated text the spelling used for the fillers in question is polyglukin and rheopolyglukin, basing on the respective usage of the terms in the abstract in English formulated (like the abstract in Russian) by the Russian Patent Office.

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Signature: Markey Milvi Vänikver
Signed this 26...day of July..2004

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РОССИЙСКОЕ АГЕНТСТВО ПО ПАТЕНТАМ И ТОВАРНЫМ ЗНАКАМ

(12) ОПИСАНИЕ ИЗОБРЕТЕНИЯ К ПАТЕНТУ РОССИЙСКОЙ ФЕДЕРАЦИИ

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- (73) Патентообладатель: Пак Владимир Николаевич

(54) СПОСОБ ЛЕЧЕНИЯ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ И КОМПЛЕКСНЫЙ ПРЕПАРАТ, ОБЛАДАЮЩИЙ ПРОТИВООПУХОЛЕВЫМ ДЕЙСТВИЕМ, ДЛЯ ОСУЩЕСТВЛЕНИЯ СПОСОБА

(57) Реферат:

Изобретение относится к медицине, а именно к онкологии. Предложено зависимости от характера и тяжести заболевания больному на фоне инфузионно-детоксикационной терапии парентерально вводить комплексный препарат, содержащий АФП в количестве 0.07-0,15 мг, полиеновый антибиотик, преимущественно амфотерицин В или нистатин, в количестве 4,2-7,0 мг и наполнитель, один раз в сутки с интервалом в три дня, курсом 10 инфузионно-капельных вливаний. Комплексный

обладающий противоопухолевым действием, содержит следующие компоненты, мг: АФП 0,07-0,15, полиеновый антибиотик 4,2-7,0, наполнитель 3,5-5,0. В качестве наполнителя преимущественно используют полисахарид из группы реополиглюкин, полиглюкин или сахар, например глюкозу. Способ позволяет снизить дозы вводимых лекарственных средств и снизить стоимость лечения. Комплексный препарат отличается повышенной эффективностью противоопухолевого действия, малокомпонентностью, простотой получения и длительным сроком хранения, 2 с. и 2 з.п. ф-лы.



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(51) Int. Cl. 7 A 61 K 38/17, A 61 P 35/00

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(12) ABSTRACT OF INVENTION

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- (24) Effective date for property rights: 22.06.2000
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- (98) Mail address: 630117, g.Novosibirsk, ul.Vjazemskaja, 2, kv.91, L.Ja.Kuchumovoj
- (71) Applicant: Pak Vladimir Nikolaevich
- (72) Inventor: Pak V.N., Pak N.A., Reshetnikov S.S., Nikonov S.D., Ogirenko A.P.
- (73) Proprietor: Pak Vladimir Nikolaevich

(54) METHOD TO TREAT MALIGNANT NEOPLASMS AND COMBINED PREPARATION OF ANTITUMOR ACTION TO PERFORM THE METHOD

(57) Abstract:

FIELD: medicine, oncology. SUBSTANCE: it is suggested as dependent upon character and severity of a disease to inject parenterally a combined AFP-containing preparation at 0.07-0.15 mg, polyenic antibiotic, predominantly amphotherycin B or nistatine at 4.2-7.0 mg and a filler, once daily at 3-d-long interval, at therapy course consisted of 10 infusion-drop injections. Combined preparation of antitumor action

contains the following components, mg: AFP 0.07-0.15, polyenic antibiotic 4.2-7.0, 3.5-5.0. filler As а filler it is predominantly used polysaccharide of rheopolyglukin, polyglukin or sugar group, for example, glucose. EFFECT: decreased doses of injected medicinal preparations and therapy cost, increased efficiency of antitumor action, decreased quantity of components, simplified production and prolonged storage period. 4 cl

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Related Articles, Links

[The effect of the initial (controlled) tonus of the arterial vessels on the correlation of arterial pressure and cardiac output during a pressor reaction to a rapid blood volume increase in rats]

[Article in Russian]

Osadchii LI, Balueva TV, Sergeev IV.

Pavlov Institute of Physiology, Russian Acad. Sci., St. Petersburg, Russia.

A considerable decrease in pressor responses to <u>polyglykine</u> at an elevated arterial tone and constant increase of cardiac output occurred in anesthetised rats. Vascular and cardiac mechanisms of the interrelationship are discussed.

PMID: 9487051 [PubMed - indexed for MEDLINE]

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Поступила 14 X 1996

РОССИЙСКИЙ ФИЗИОЛОГИЧЕСКИЙ ЖУРНАЛ ЦМ. И. М.

formerly I. M. Sechenov Physiological Journal) RUSSIAN JOURNAL OF PHYSIOLOGY

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Appendix

ВЛИЯНИЕ ИСХОДНОГО (УПРАВЛЯЕМОГО) ТОНУСА АРТЕРИАЛЬНЫХ сосудов на соотношение артериального давления и сердечного выброса при прессорной реакции на быстрое увеличение объема крови у крыс

ФЛ. И. Осадчий, Т. В. Балуева, И. В. Сергеев

И. П. Павлова РАН, Россия, 199034, Санкт-Петербург, наб. Макарова, б Лаборатория физиологии кровообращения Института физиологии им.

более низкого давления. В основе данной зависимости, по-видимому, лежит сосудистый В опытах на наркотизированных крысах исследовали изменение взаимоотношений между сердечным выбросом и артериальным давлением в процессе формирования прессорной реакции тонуса (в дивпазоне среднего артериального давления от уровня выше 90 до 165 мм рт. ст.) сохранении в половиие наблюдений такого же прироста сердечного выброса, как и на фоне на внутривенное введение 0.5 мл полиглюкина при различном исходном (управлясмом ангиотензином-2) тонусе артериальных сосудов. Установлено, что на фоне повышенного исходного наблюдалось существенное (в 4 раза) уменьшение прессорных эффектов полиглюкина механизм, связанный с повышением трансмурального давления в артериальной системе.

Ключевые слова: полиглюкин, ангиотензин-II, среднее артериальное давление, сердечный

L. Osadchiv, T. V. Balueva and I. V. Sergeev THE EFFECT OF INITIAL (CONTROLLABLE) TONE OF ARTERIAL VESSELS ON RELATIONSHIP BETWEEN ARTERIAL PRESSURE AND CARDIAC OUTPUT DURING PRESSURE RESPONSES TO A FAST INCREASE IN THE BLOOD VOLUME, Pavlov Institute of Physiology of the Russian Acad. Sci., 199034, St. Petersburg. Nab. Makarova, 6, Russia.

A considerable decrease in pressor responses to polyglykine at an elevated arterial tone and constant increase of cardiac output occurred in anesthetised rats. Vascular and cardiac mechanisms of the interrelationship are discussed.

Key words: polyglykine, angiotensin-2, arterlal pressure, cardiac output.

В предыдущих исследованиях нами была установлена обративя прямолинейная зависимость величины прессорных реакций, вызываемых быстрым введением плазмозаменителя (полиглюхина) и агониста с-адренорецепторов, от исходного спонтанного [7] и управляемого [10] тонуса артериальных сосудов у крыс. Интерес к этой проблеме усиливается в связи с исследованиями, выполненными под руководством . П. Конради, в которых установлена зависимость местных реакций в различных обнаружены влияния трансмурального давления и нейрогуморального компонента тонуса на вазомоторные реакции сосудов конечности у крыс [1,11,12,16] и лягушск Исследований по данной проблеме, выполненных на системном уровне, в сосудистых областях от величины исходного тонуса сосудов [1]. Кроме того, поступной литературе нами не обнаружено.

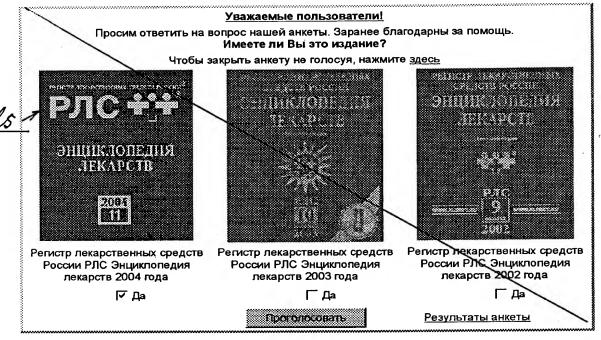
исходного тонуса артериальных сосудов неизбежно ведет к увеличению постнагрузки на сердце, в связи с чем прессорную реакцию от введения полиглюкина можно рассматривать как дополнительную постнагрузку, что может влиять на величину сердечного выброса (* 3). Во-вторых, в этих реакциях возможно участие сосудистого Нами [10] было выдвинуто предположение о том, что, во-первых,

Энциклопедия лекарств. Полиглюкин сухой субст.-пор. 1,5 кг; бан. 3 л; ? 71/609/31; произв.: ... Page 1 of

> Поиск препаратов > Все препараты ТН > Описание препарата

Полиглюкин сухой

субст.-пор. 1,5 кг; бан. 3 л; №71/609/31; произв.: Биохимик (Россия); код EAN:4602509005225



Appendix 6A

Латинское название: Polyglucinum siccum Действующее вещество: Декстран* (Dextran*)

Фармакологические группы: Детоксицирующие средства, включая антидоты. Заменители

плазмы и других компонентов крови

Срок годности: 7 лет

Условия хранения: При температуре от -10 до 20 °C

Уважаемые пользователи! Обращаем Ваше внимание, что издательство РЛС не сертифицирует, не проводит независимый анализ предоставленной в используемых источниках информации, не рекомендует и не отстаивает ни один из публикуемых продуктов и не может взять на себя ответственность за их неправильное применение и связанные с этим негативные последствия.

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Appendix 6B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on appendix 6A, a web site of the register of medicinal agents of Russia: (rls), and that the paragraphs not translated are not relevant.

Polyglucin* dry

substance, powder 1.5 kg; a jar of 3 l; No.71/609/31; producer: Biohimik (Russia); code EAN: 4602509005225

Name in Latin: Polyglucinum siccum

Active substance: Dextran

Pharmacological groups: Detoxicating agents, including antidotes. Substitutes of plasma and other

blood components.

Term of validity: 7 years

Conditions of storage: At temperature of 10-25°C

* Note: The spelling in English, being in line with the given spelling in Latin.

Signature: Marthy Milvi Vänikver
Signed this 26 th day of July 2004

> Поиск препаратов > Все препараты ТН > Описание препарата

Реополиглюкин сухой

субст.-пор.; бан. 1 кг; №79/702/2; произв.: Красфарма (Россия); код EAN:4602521000987



Appendix 7A

Латинское название: Rheopoluglucinum siccum Действующее вещество: Декстран* (Dextran*)

Фармакологические группы: Детоксицирующие средства, включая антидоты. Заменители

плазмы и других компонентов крови

Срок годности: 5 лет

Условия хранения: В сухом месте, при температуре 10-25 °C

Уважаемые пользователи! Обращаем Ваше внимание, что издательство РЛС не сертифицирует, не проводит независимый анализ предоставленной в используемых источниках информации, не рекомендует и не отствивает ни один из публикуемых продуктов и не может взять на себя ответственность за их неправильное применение и связанные с этим негативные последствия.

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Appendix 7B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on appendix 7A, a web site of the register of medicinal agents of Russia:(rls), and that the paragraphs not translated are not relevant.

Rheopolyglucin* dry

substance, powder; a jar of 1.5 kg; No. 79/702/2; producer: Biohimik (Russia); code EAN: 4602509005249

Name in Latin: Rheopolyglucinum siccum

Active substance: Dextran

Pharmacological groups: Detoxicating agents, including antidotes. Substitutes of plasma and other

blood components.

Term of validity: 5 years

Conditions of storage: In dry place at temperature of 10-25°C

* Note: The spelling in English, being in line with the given spelling in Latin.

Signature: Markoy Milvi Vänikver

Signed this 26 th day of July 2004



средняя

Appendix 8A, page 1

Recipe.Ru: фармацевтический информационный сайт

<u>В</u> Избраниое! | Сделать схартовой!

				\mathcal{L}			стартовой!
Началь	Списки: Лекспел	ства - Фирмі	ы · Страны · Фа	рмакологическа	g rnynna · Co	ACTUR BO KON	
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	Расширенный п		'				
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Прайс-листы	Декстран, средняя						}
Ресурсы »	молекулярная	Полиглюкин	ı			субстанция-	1 /
Поиск	масса 50000- 70000 (Dextran,	сухой (Polyglucin	Россия	Не указано	71/609/31	порошок аморфный	Отобразить
Услуги ∀	average	siccum)				(банки 10 л)	
Форуны »	molecular weight 50000-70000)	•				,	
Подписка	Декстран,						
Гостевая книга	средняя молекулярная	Полиглюкин	•			субстанция-	- [
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E-mail	70000 (Dextran,	(Polyglucin	Россия	Не указано	71/609/31	аморфный	Отобразить
	average	siccum)				(банки 3 л)	
	molecular weight 50000-70000)						
V	Декстран,						1
	средняя						\
	молекулярная	Полиглюкин	I			субстанция-	
	масса 50000- 70000 (Dextran,	сухой (Polyglucin	Россия	Не указано	71/609/31	порошок аморфный	Отобразить
	average	siccum)				(банки 5 л)	
	molecular weight	,				(55,000)	1
	50000-70000)						ļ
	Декстран, средняя						
	молекулярная	Полиглюкин				субстанция-	1
	масса 50000-	сухой	Россия	<u> Биохимик ОАО</u>	71/609/31	порошок	Отобразить
	70000 (Dextran,	(Polyglucin		(Саранск)	7 17005751	аморфный	0.000
	average molecular weight	siccum)				(банки 10 л)	
	50000-70000)						
	Декстран,						1
	средняя	Попистон					- 1
	молекулярная масса 50000-	Полиглюкин сухой		Биохимик ОАО		субстанция- порошок	
	70000 (Dextran,	(Polyglucin	Россия	(Саранск)	71/609/31	аморфный	Отобразить
	average	siccum)				(банки 3 л)	
	molecular weight 50000-70000)						
	Декстран,						
	monorpan,						

мацевтический и	нформацио	нный сайт		•		Page 2 of
молекулярная масса 50000- 70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	н <u>Россия</u>	Appendix 8A, р Биохимик ОАО (Саранск)	page 2 71/609/31	субстанция- порошок аморфный (банки 5 л)	Отобразить
Декстран, средняя молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000) Декстран,	Полиглюкин сухой (Polyglucin siccum)	1 <u>Россия</u>	Красфарма ОАО	71/609/31	субстанция порошок аморфный (банки 10 л)	Отобразить
средняя молекулярная масса 50000- 70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	1 <u>Россия</u>	Красфарма ОАО	71/609/31	субстанция порошок аморфный (банки 3 л)	Отобразить
Декстран, средняя молекулярная масса 50000- 70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	н <u>Россия</u>	<u>Красфарма</u> <u>ОАО</u>	71/609/31	субстанция порошок аморфный (банки 5 л)	Отобразить
Вернуться к сводной таблице Отправить по е-mail Легенда						
Поиск: ИСКАТЬ!						для печат
Полиглюкин сухой (Polyglucin siccum) международное название						
Декстран,		<u>.</u> Юлекулярная м	acca 50000-70	000 (Dextrar	a. average	molecular
Декстран, средняя молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000)						
ТОРГОВОЕ НАЗВАНИЕ Полиглюкин сухой (Polyglucin siccum)						
СТРАНА-ПРОИЗВОДИТЕЛЬ Россия						
НОМЕР РЕГИСТРАЦИИ ПРЕПАРАТА						
71/609/31 ФОРМЫ ВЫПУСКА субстанция-порошок аморфный (банки 10 л) ФАРМАКОЛОГИЧЕСКАЯ ГРУППА						
плазмозамещающее средство ФАРМАКОЛОГИЧЕСКАЯ ГРУППА ПО АТК						
В05AA05 Декстран (Dextran)					ļ	
ФАРМАКОЛОГИЧЕСКОЕ ДЕЙСТВИЕ восполняющее ОЦК						
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противошоковое

плазмозамещающее

дезинтоксикационное

КОДЫ ТН ВЭД СНГ

2940 00 900 0

3002 90 100 0

INGREDIENTSTEXT ИЗ ОСНОВНОЙ ТАБЛИЦЫ

декстран, средняя молекулярная масса 50-70 тыс. - 1 л

ЛЕКАРСТВЕННАЯ ФОРМА

субстанция - порошок аморфный

ФОРМА ВЫПУСКА

банки

РАЗДЕЛ БАЗЫ

Субстанции, стандартные образцы лекарственных средств и вспомогательные вещества

Recipe Ru: Фармацевтический информационный сайт

<u>СОСТАВ ПО КОМПОНЕНТАМ</u> декстран

Appendix 8A, page 3

Script version: 1.0.0-RC

Recipe.Ru | Идея и дизайн: Дмитрий Шкатов (c) 1999-2004

E-mail | 🚜 ICQ | Вверх

Начало | Новости | Прайс—листы | Документы | Литература | Ресурсы | Услуги | Программы | Заказ CD | Ссылки | Форумы | Подписка

Реклама на www.recipe.ru

Page 3 of

Appendix 8B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on pages 1-3 of appendix 8A, the web sites of Recipe.ru: pharmaceutical informational site, and that the paragraphs thereof not translated are not relevant.

Recipe.Ru: Pharmaceutical informational site

International name	Trade name	Country- producer	The firm- producer	Preparation registration number	Output form
Dextran, average molecular weight 50000-70000		Russia	not indi- cated	71/609/31	substance- amorphous powder (jars of 10 l)
Dextran, average molecular weight 50000-70000		Russia	not indi- cated	71/609/31	substance- amorphous powder (jars of 3 l)
Dextran, average molecular weight 50000-70000		Russia	not indi- cated	71/609/31	substance- amorphous powder (jars of 5 l)
Dextran, average molecular weight 50000-70000	• •	Russia	Biohimik (Saransk)	71/609/31	substance- amorphous powder (jars of 10 l)
Dextran, average molecular weight 50000-70000		Russia	Biohimik (Saransk)	71/609/31	substance- amorphous powder (jars of 3 1)
Dextran, average molecular weight 50000-70000		Russia-	Biohimik (Saransk)	71/609/31	substance- amorphous powder (jars of 5 l)
Dextran, average molecular weight 50000-70000		Russia	Kraspharma	71/609/31	substance- amorphous powder (jars of 10 l)
Dextran, average molecular weight 50000-70000		Russia	Kraspharma	71/609/31	substance- amorphous powder (jars of 3 l)
Dextran, average molecular weight 50000-70000		Russia	Kraspharma	71/609/31	substance- amorphous powder (jars of 5 l)

Polyglucin dry (Polyglucin siccum*)

International name

Dextran, average molecular weight 50000-70000

Trade name

Polyglucin dry (Polyglucin siccum*)

Country-producer

Russia

Preparation registration number

71/609/31

Output form

substance - amorphous powder (jars of 10 l)

Pharmacological group

plasma substituter

Pharmacological group according to ATC**

B05AA05 Dextran

Pharmacological effect

filling to CBV***

antiaggregative

antishock effect

plasma substituting

desintoxicating

Codes****

2940 00 900 0

3002 90 100 0

Cmposition from the text of the main table

Dextran, average molecular weight 50000-70000, page 1

Medicinal form

substance - amorphous powder

Output form

jars

Section of the base

Substances, standard examples of medicinal agents and auxiliary substances

Composition according to the components

Dextran

Notes:

- * The English translation in the brackets is incorrect because the first word *Polyglucin* is in English whereas the second word *siccum* is in Latin
- ** ATC the anatomical therapeutic chemical classification
- *** CBV circulating blood volume
- **** Codes in Russian, not relevant

Signature: Markey Milvi Vänikver Signed this 26 th day of July 2004



30/07/2004 Михаил Зурабов: Бесплатную медицину в России никто не отменит

Appendix 9A, page 1

Recipe.Ru: фармацевтический информационный сайт

<u>В</u> Избранное! | <u>Сделать</u> |стартовой!

				J		c	тартовой!
Начало	Списки: Лекспело	тва - Фирмы - С	тпаны - Фапмак	ологическая гру	яна · Состав	по компон	
О проекте	ТН ВЭД СНГ : Фа				1		
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	базы : Показания		,,,,,,	·	, , ,,		
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Прайс-листы	Декстран, средняя					_	\ \
Ресурсы **	молекулярная	Реополиглюки	1			субстанци порошок	IR-
Поиск	масса 30000-	сухой	Россия	Не указано	79/702/2		й Стобраз
1	40000 (Dextran, average	(Rheopolyglukir siccum)	<u> </u>	•		(банки 3 л	
	molecular weight					300-500 r/	Л
Форуны »	30000-40000)						l l
Подписка	Декстран, средняя						1
Гостевая книга	молекулярная	Реополиглюки	1			субстанци порошок	IЯ-
Обратная связь	масса 30000-	сухой	Россия	Не указано	79/702/2	аморфны	й Отобраз
E-mail	40000 (Dextran, average	(Rheopolyglukir siccum)		, ,		(банки 5 л	1)
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1	Декстран, средняя						\
	молекулярная	Реополиглюки	1			субстанци	ія-
	масса 30000-	сухой	Россия	Не указано	79/702/2	порошок аморфны	й Отобраз
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	30000-40000)						
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	масса 30000-	сухой	Россия	Биохимик ОАО	79/702/2	порошок аморфны	й Отобраз
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	average molecular weight	siccum)				300-500 г	/л
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	средняя молекулярная	Реополиглюки	4			субстанці	ля -
	масса 30000-	сухой	Россия	Биохимик ОАО	79/702/2	порошок	й Отобраз
	40000 (Dextran,	(Rheopolyglukir	1	(Саранск)	19/1022	(банки 5 л	
	average molecular weight	siccum)				300-500 г	/n /
	30000-40000)						
	Декстран,						
	средняя					субстанці	ля -

Субстанции, стандартные образцы лекарственных средств и вспомогательные вещества

РАЗДЕЛ БАЗЫ

СОСТАВ ПО КОМПОНЕНТАМ

Appendix 9A, page 3

декстран

ОПИСАНИЕ

Белый аморфный порошок без запаха. Реополиглюкин сухой представляет собой полисахариддекстра с молекулярным весом 30 000 — 40 000 и предназначается для приготовления препарата реополиглюкина.

УСЛОВИЯ ХРАНЕНИЯ

В сухом месте при температуре не ниже +10град.С и не выше +25град.С.

СРОК ГОДНОСТИ

4 года.

Script version: 1.0.0

Recipe.Ru | Идея и дизайн: Дмитрий Шкатов (c) 1999-2004

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Реклама на www.recipe.ru

Appendix 9B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on pages 1-3 of appendix 9A, the web sites of Recipe.ru: pharmaceutical informational site, and that the paragraphs thereof not translated are not relevant.

Recipe.Ru: Pharmaceutical informational site

International name		Country- producer	The firm- producer	Preparation registration number	Output form
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	not indi- cated	79/702/2	substance- amorphous powder (jars of 3 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	not indi- cated	79/702/2	substance- amorphous powder (jars of 5 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	not indi- cated	79/702/2	substance- amorphous powder (jars of 10 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	Biohimik (Saransk)	79/702/2	substance- amorphous powder (jars of 3 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	Biohimik (Saransk)	79/702/2	substance- amorphous powder (jars of 5 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	Biohimik (Saransk)	79/702/2	substance- amorphous powder (jars of 10 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	Kraspharma	79/702/2	substance- amorphous powder (jars of 3 l)

Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin	Russia	Kraspharma	79/702/2	300-500 g/l substance- amorphous powder
	siccum)				(jars of 5 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglu- cin dry (Rheo- polyglukin siccum)	Russia	Kraspharma	79/702/2	substance- amorphous powder (jars of 10 l) 300-500 g/l

Rheopolyglucin dry (Rheopolyglukin siccum*)

International name

Dextran, average molecular weight 30000-40000

Trade name

Rheopolyglucin dry (Rheopolyglukin siccum*)

Country-producer

Russia

Preparation registration number

79/702/2

Output form

substance - amorphous powder (jars of 3 l), 300-500 g/l

Pharmacological group

plasma substituter

Pharmacological group according to ATC**

B05AA05 Dextran

Pharmacological effect

filling to CBV***

antiaggregative

antishock effect

plasma substituting

desintoxicating

Codes****

2940 00 900 0

3002 90 100 0

Composition from the text of the main table

Dextran, average molecular weight 30000-40000, page 1

Medicinal form

substance - amorphous powder

Output form

jars

Section of the base

Substances, standard examples of medicinal agents and auxiliary substances

Composition according to the components

Dextran

Description

White amorphous odourless powder. Dry rheopolyglucin is a polysaccharide dextran of molecular weight 30000-40000 and is intended for the preparation of rheopolyglucin solution.

Conditions of storage

In dry place at temperature of not less than 10°C and not higher than 25°C.

Term of validity

4 years

Notes:

- The English translation in the brackets is incorrect because the first word Rheopolyglukin is in English whereas the second word siccum is in Latin.
- ** ATC the anatomical therapeutic chemical classification
- *** CBV circulating blood volume
- **** Codes in Russian, not relevant

Signature: Markey Milvi Vänikver
Signed this 26 day of July 2004

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